injured tissue comprises administering to said ~~mammal~~ human an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen having an amino acid sequence selected from at least one of

(a) an amino acid sequence sharing at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, amino acids 38-139 of SEQ ID NO: 5,

(b) an amino acid sequence having greater than 60% amino acid identity with the C-terminal seven-cysteine skeleton of human OP-1, amino acids 38-139 of SEQ ID NO: 5,

(c) an amino acid sequence defined by Generic Sequences 1, 2, 3, 4, 5 or 6 (SEQ ID NOs: 1, 2, 3, 4, 30 or 31), or

(d) an amino acid sequence defined by OPX (SEQ ID NO: 29).

49. (**Amended**) A method for reducing tissue damage associated with hyperoxia injury in a human, the method comprising the step of providing to an injured tissue a therapeutic concentration of a morphogen sufficient to alleviate the damage associated with said injury, wherein said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises administering to said ~~mammal~~ human an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen having an amino acid sequence selected from at least one of

(a) an amino acid sequence sharing at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, amino acids 38-139 of SEQ ID NO: 5,

(b) an amino acid sequence having greater than 60% amino acid identity with the C-terminal seven-cysteine skeleton of human OP-1, amino acids 38-139 of SEQ ID NO: 5,

(c) an amino acid sequence defined by Generic Sequences 1, 2, 3, 4, 5 or 6 (SEQ ID NOs: 1, 2, 3, 4, 30 or 31), or

(d) an amino acid sequence defined by OPX (SEQ ID NO: 29).

REMARKS

Claims 2, 23 and 49 are pending and currently under consideration. Applicants add new claims 50-70. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration

in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note with appreciation that the preliminary amendment filed June 20, 2000 has been entered in full.

In the Official Action of January 28, 2002, the drawings were objected to as containing certain informalities. Applicants are currently in the process of reviewing the objections to the drawings, and will prepare formal drawings shortly.

Claims 3, 23 and 49 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement and as failing to provide an adequate written description of the invention in the specification. In particular, the Examiner has objected to the phrase "an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen", since the particular morphogens are not specified in the claims. This ground of rejection is respectfully traversed as applied to the amended claims.

Applicants contend that the specification provides ample support for the claimed subject matter. By way of example, Applicants direct the Examiner to page 39, lines 9-20; page 54, lines 22-25; and page 57, line 27-page 58, line 11 which support the adequate description of the claimed subject matter.

> "Provided below are detailed descriptions of suitable morphogens useful in the methods and compositions of this invention, as well as methods for their administration and application, and numerous, nonlimiting examples which 1) illustrate the suitability of the morphogens and morphogen-stimulating agents described herein as therapeutic agents for protecting tissue from the tissue destructive effects associated with the body's inflammatory response; and 2) provide assays with which to test candidate morphogens and morphogen-stimulating agents for their efficacy." (page 39, lines 9-20).
>
> "Alternatively, administration of an agent capable of stimulating morphogen expression and/or secretion in vivo, preferably at the site of injury, also may be used." (page 54, lines 22-25).
>
> "Alternatively, an effective amount of an agent capable of stimulating endogenous morphogen levels may be administered by any of the routes described above. For example, an agent capable of stimulating

> morphogen production and/or secretion from cells of affected tissue or a transplanted organ may be provided to a mammal, e.g., by direct administration of the morphogen to the tissue or organ. A method for identifying and testing agents capable of modulating the levels of endogenous morphogens in a given tissue is described generally herein in Example 15, and in detail in copending USSN 752,859, filed August 30, 1991, the disclosure of which is incorporated herein by reference. Briefly, candidate compounds can be identified and tested by incubating the compound in vitro with a test tissue or cells thereof, for a time sufficient to allow the compound to affect the production, i.e., the expression and/or secretion, of a morphogen produced by the cells of that tissue." (page 57, line 27-page 58, line 11).

Example 15 details a method to identify agents suitable for use in the present invention. When viewed in light of the rest of the specification which provides morphogens, methods of detecting the expression of said morphogens in cells and tissues, and methods of using morphogens to treat various conditions (Examples 1-14), the teachings of Example 15 satisfy the requirement under 35 U.S.C. 112, first paragraph, and provide both an adequate written description of the invention and enable one of skill in the art to practice the invention.

The office action contends that Applicants have not described an agent suitable for practicing the methods of the present invention. This is presented as the basis of both grounds of rejection of the pending claims. Applicants refer to the guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (Federal Register Vol. 66, No. 4, page 1106, column 1). As of the effective filing date of the present application (1995), the state of the art provided agents which induced expression of TGFβ family members. By way of example, Applicants cite the teachings of Laufer et al. (1994), Wall and Hogan (1994), and Roberts et al. (1995) to demonstrate that one of skill in the art was aware of factors which induce TGFβ expression in vivo (enclosed herewith as Exhibits 1-3).

Laufer et al. established that the development of the limb bud is dependent on interactions between hedgehog, FGF, and BMP. "BMP-2 expression in both the mesoderm and ectoderm is thus a downstream target of Sonic hedgehog activity in the mesoderm. In contrast with the expression domains of the Hoxd genes, the endogenous and ectopic BMP-2 expression domains correlate well with those of Sonic hedgehog. This suggests that BMP-2 expression is

regulated more directly by Sonic hedgehog than is expression of the Hoxd genes." (pg 996, column 2).

Roberts et al. demonstrate a similar relationship between hedgehog and BMP in the gut. "Sonic can induce ectopic BMP-4, Hoxd-11 and Hoxd-13 expression in the mesoderm after infection of both ectodermal and mesodermal tissue." (pg 3168, column 1). These two references are among many which demonstrate that expression of a hedgehog family member induces the expression of a BMP family member. The two examples provided here demonstrate that this inductive influence occurs in multiple tissues, and that hedgehog can induce the expression of several BMP family members.

Finally, Applicants refer to a review by Wall and Hogan which demonstrates that, as of the effective filing date of the present application, the interrelationship between TGFβ family members and other factors was well established in both invertebrate and vertebrate systems.

> "these studies raise the possibility that dpp regulates and is regulated by two other secreted growth factors, encoded by wingless (wg) and hedgehog (hh). As both hh and wg-type (Wnt) genes exist in vertebrates, work on dpp in Drosophila provides an important paradigm for the understanding of TGFβ related gene function in higher organisms." (page 518, column 1).
>
> "During midgut development, DPP is made in the visceral mesoderm and induces changes in gene expression in the adjacent endoderm, thus providing a model for understanding epithelial/mesenchymal interactions in higher organisms. Studies have shown that dpp transcription in the mesoderm is activated by the HOM gene Ultrabithorax (Ubx) and repressed by Abdominal-A (Abd-A). In both cases, regulation is direct and involves multiple DNA-binding sites in a 5' upstream region of dpp. In the endoderm, DPP switches on the HOM gene labial, which has a DPP-response element in its 5' upsteam region. These studies clearly show that dpp acts during development both upstream and downstream of homeotic genes." (page 518, column 2).
>
> "Studies on eye morphogenesis demonstrate yet another key role for dpp during Drosophila development. In this case, dpp is expressed in the morphogenetic furrow, a wave of organizing activity that moves across the eye imaginal disc. Transcription of dpp is regulated by the extracellular signaling molecule encoded by hh, and DPP induces morphogenesis in front of the furrow. In the leg disc, dpp is also

> regulated by hh and cooperates with wg in the regulation of the homeobox gene aristaless, which then acts as an organizer for proximal/distal patterning. In this case, at least three signaling molecules, hh, DPP, and Wg, coordinate to generate patterning in an epithelial sheet" (page 518, column 2).
>
> "Genetic and functional studies support the idea that TGFβ related proteins mediate these events by acting upstream and downstream of transcription factors and other growth factors." (page 520, column 2).

Wall and Hogan show that one of skill in the art clearly recognized that the expression of TGFβ family members is induced by other factors, and that TGFβ family members in turn modulate the expression of still other factors.

Exhibits 1-3 demonstrate that one of skill in the art would readily appreciate the existence of agents which stimulate TGFβ gene expression. In fact, these articles demonstrate that such agents had already been identified, that these agents were well known in the art, and accordingly that such agents need not be explicitly described by Applicants.

Furthermore, Applicants point out that the claims are directed to methods of using agents which induce expression of a morphogen. The invention is not directed to the agents themselves. This clearly distinguishes the present fact pattern from that presented in the cases cited by the Examiner. The pending claims clearly detail the methods of the present invention, and provide a detailed description of the characteristics of the agents used in these methods. Accordingly, one of skill in the art can readily envision the agents for use in practicing the methods of the invention.

Applicants additionally contend that these references establish that one of skill in the art could reasonably expect to identify factors which induce expression of the morphogens described in the specification. In stating the reasons for rejecting the pending claims for allegedly failing to be enabled throughout their scope, the Office Action states that "[t]he specification does not disclose any such agents. No suitable screening for such agents are disclosed." As outlined in detail above, Applicants clearly disagree on both counts. The specification has provided a detailed example (Example 15) of a method that can be used to screen for agents to be used in the methods of the present invention. Furthermore, the art is replete with references that demonstrate the existence of agents which induce expression of TGFβ family members and

BMPs in particular. Applicants contend that this fact pattern clearly distinguishes the present invention from that of the cases cited by the Examiner. The art clearly discloses agents which meet the limitations of the pending claims, and the specification clearly outlines an approach to identify further agents. Armed with knowledge in the art and the specification, one of skill in the art could reasonably expect to identify agents used to practice the present invention. Accordingly, Applicants contend that the claims are enabled throughout their scope, and that the claims satisfy all of the requirements for adequate written description.

Although Applicants contend that the claims satisfy all of the requirements of 35 U.S.C. 112, first paragraph, Applicants have amended the claims to more explicitly point out the claimed morphogens. Such amendments are made only to expedite prosecution, and Applicants reserve the right to prosecute claims of similar or differing scope. In light of Applicants' amendments, and the arguments of record, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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